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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,239	02/18/2004	William Douglas Cress JR.	1372.133.PRC	2238

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/708,239	CRESS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *6-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of group I, claims 1-5, in the reply filed on August 5, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 5, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation "the downregulation of E2F1" in line 4. There is insufficient antecedent basis for this limitation in the claim. Claim 4 recites the limitation "the repression of E2F1" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. This claim recites use of an "RNA inhibitor molecule". This phrase renders the claim indefinite because it is unknown whether this phrase is meant to encompass molecules that inhibit RNA or if it is meant to encompass inhibitors that are composed of RNA.

Claim 5 is rejected under 35 U.S.C. 1 12, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites that the RNA inhibitor molecules is "a BS/U6 E2F1 RNAi plasmid". This designation is not a term of art and is indefinite because one of skill in the art would not recognize the structure of the plasmid identified by this abbreviation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is directed to a method of modulating apoptosis by regulating the expression of E2F1. Claims 2 and 3 limit claim 1 by stating the apoptosis is flavopiridol-induced and the apoptosis is reduced by repression of E2F1. Claim 4 limits claim 1 to

the use of an RNA inhibitor molecule, while claim 5 states the RNA inhibitor molecule is a BS/U6 E2F1 RNAi plasmid.

Claim 1 has as the sole active step "regulation of expression of E2F1", a scope that encompasses both upregulation and downregulation. Additionally, the claimed method encompasses indirect regulation of E2F1 expression through modulation of other genes that can affect expression of E2F1. This method encompasses use of a large genus of compounds that are agents capable of directly or indirectly inhibiting or activating E2F1 expression. Such agents include nucleic acids, proteins, antibodies and small organic molecules. In order to perform the claimed method throughout its full scope, one would have to find inhibitors/activators of E2F1 and then determine which of these agents will affect expression of Mcl-1. This process would have to be repeated for all genes whose expression could affect expression of E2F1. The species disclosed in the specification are not representative of the genus because the genus is highly variant.

The specification describes a single plasmid expressing a stem-loop RNA that decreases the expression of E2F1 and reduces apoptosis. The specification does not describe the structure of any other inhibitors of E2F1 nor does it describe the structure of any molecule that upregulates E2F1 expression. The specification does not describe the structure of any agents that indirectly regulates E2F1 expression. The prior art does not provide the sufficient examples of structures capable of performing the function of directly or indirectly modulating expression of E2F1.

The skilled artisan cannot envision the detailed structure of the encompassed modulating agents, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, while the specification provides adequate description of a plasmid that produces a single nucleic acid inhibitor of E2F1, the full breadth of the many types of possible modulators encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulation of apoptosis through inhibition of expression of E2F1 in cells *in vitro*, does not reasonably provide enablement for modulation of apoptosis by direct or indirect regulation of expression of E2F1 using any agent *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples

and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Given the breadth of claim 1 as described in the previous rejection, one of skill in the art would not be able to perform the claimed method without undue experimentation. In order to perform the method of claim 1, one of skill in the art would need to first determine what molecules are inhibitors/activators of E2F1 or are inhibitors/activators of genes that can indirectly affect E2F1 expression and then determine which of these agents affect expression of Mcl-1.

Additionally, claim 5 is directed to the method of claim 1 performed with a nucleic acid inhibitor of E2F1. The state of the prior art is such that use of nucleic acids to inhibit gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression with nucleic acids at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol. 6, p 72-81), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514) and Jen et al. (Stem Cells 2000, vol. 18, p 307-319)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect.

Jen et al. state (see page 313, second column, second paragraph)

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the

application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides one example of the use of a nucleic acid to inhibit E2F1 expression in several cell lines, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states

"The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide."

Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The field of nucleic acid therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for methods of modulating apoptosis using nucleic acids to directly or indirectly regulate expression of E2F1 as the art of inhibiting gene expression by introducing nucleic acids into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized, including 1). the mode of delivery of the nucleic acid to an organism that would allow it to reach the targeted cell, 2). the amount of nucleic acid that would need to be delivered in order to bind a sufficient amount of E2F1 to modulate apoptosis once it reached the proper cell and 3). ensuring the nucleic acid remains viable in a cell for a period of time that allows

modulation of apoptosis to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each nucleic acid. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-5 are not enabled.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Calabretta et al. (WO 95/24223).

Claim 1 is directed to a method of modulating apoptosis in a cell by regulating the expression of E2F1. Claim 2 limits the method of claim 1 to modulation of apoptosis induced by Flavopiridol. Claim 3 limits claim 1 to downregulation of E2F1 while claim 4 states the repression occurs through use of an RNA inhibitor molecule.

Calabretta et al. disclose antisense oligonucleotides targeted to E2F1 that inhibit expression of E2F1. Calabretta et al. further disclose that these antisense oligonucleotides modulate cell proliferation. Although the oligonucleotides of Calabretta

et al. are not disclosed as modulating apoptosis, these oligonucleotides regulate E2F1 expression and would necessarily modulate apoptosis, including flavopiridol-induced apoptosis.

Thus, Calabretta et al. disclose all limitations of and anticipate claims 1-4.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Grassi et al. (Antisense & Nucleic Acid Drug Development 2001, vol. 11, pages 271-287).

Claim 1 is directed to a method of modulating apoptosis in a cell by regulating the expression of E2F1. Claim 2 limits the method of claim 1 to modulation of apoptosis induced by Flavopiridol. Claim 3 limits claim 1 to downregulation of E2F1 while claim 4 states the repression occurs through use of an RNA inhibitor molecule.

Grassi et al. disclose hammerhead ribozymes targeted to E2F1 that inhibit expression of E2F1. Grassi et al. further disclose that these ribozymes decrease proliferation of vascular smooth muscle cells. Although the ribozymes of Grassi et al. are not disclosed as modulating apoptosis, the ribozymes regulate E2F1 expression and would necessarily modulate apoptosis, including flavopiridol-induced apoptosis.

Thus, Grassi et al. disclose all limitations of and anticipate claims 1-4.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Adachi et al. (Oncogene 2002, vol. 21, pages 87-95).

Claim 1 is directed to a method of modulating apoptosis in a cell by regulating the expression of E2F1. Claim 2 limits the method of claim 1 to modulation of apoptosis

induced by Flavopiridol. Claim 3 limits claim 1 to downregulation of E2F1 while claim 4 states the repression occurs through use of an RNA inhibitor molecule.

Adachi et al. disclose on page 88, column 2 that antisense oligonucleotide targeted to uPAR decreases expression of E2F1. Adachi et al. further disclose on page 92, column 1 that cells transfected with this antisense oligonucleotide become apoptotic. Thus, antisense oligonucleotides targeted to uPAR indirectly downregulate E2F1 expression and modulate apoptosis. Adachi et al. do not disclose that uPAR antisense oligonucleotides modulate Flavopiridol-induced apoptosis but these oligonucleotides indirectly regulate E2F1 expression and thus would necessarily modulate apoptosis induced by Flavopiridol.

Thus, Adachi et al. disclose all limitations of and anticipate claims 1-4.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
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TV
October 17, 2005

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PATENT EXAMINER